REMARKS

Claims 1, 102, 105 and 106 are under consideration. Claim 1 has been canceled without prejudice to the subject matter therein. The specification has been amended to add references to sequence identifications (SEQ ID NOs) that match the sequences in the original specification and do not add new matter.

Election/Restriction

On page 2 of the Office Action, the Examiner points out that a previously issued restriction requirement had resulted in the selection of species including SEQ ID NO:124, and by deleting that limitation from claim 1 by amendment, the Applicants had "switched inventions." Applicants have canceled claim 1 in accordance with the Examiner's withdrawal of that claim.

Priority

On pages 3-4 of the Action, the Examiner notes the error in submitting the Application Data Sheet with the incorrect title. Applicants submit a Supplemental Application Data sheet herewith.

Specification

On page 4 of the Action, the Examiner requires correction of "sections 0019,0127" to include the "SEQ ID NO:" identifier. Applicants have amended the specification in accord.

Rejection under 35 U.S.C. § 102

On page 5 of the Office Action, the Examiner rejects claims 102 and 105-106 under 35 U.S.C. § 102(a) "as anticipated by Kalstad et al. (Proceedings of the Second Joint EMBS/BMES Conference Oct 23-26, 2002…)." Applicants respectfully traverse the rejection.

The present invention is a CIP of application Ser. No. 10/295,734, filed Nov. 15, 2002; which in turn claims the benefit of provisional application Ser. No. 60/332,746, filed Nov. 16, 2001. A Supplemental Application Data Sheet is filed herewith, and a copy of this paper is supplied for the Examiner. The priority date of the present application is November 16, 2001, the filing date of the provisional application.

Further regarding the provisional application from which the present application derives, the sequence CNAFKILVVITDGEK is disclosed in the provisional application at, for example, page 6. The sequence was linked to a hydrophilic polymer (dextran), and this bioconjugate dramatically

reduced inflammatory adhesion. Please note also that the hydrophilic polymers are discussed on page 4 of the provisional application. The provisional application also provides, for example at page 5, support for a peptide based on the ICAM-1 binding pocket (A domain) of CD11b/CD18 covalently conjugated to dextran.

Hence, the Kalstad reference is not applicable as a § 102(a) reference, and the rejection may be withdrawn.

Rejection under 35 U.S.C. § 103

Next, on pages 6-10 of the Action, the Examiner rejects claims 102, and 105-106 under 35 U.S.C. § 103(a) "as being unpatentable over Rieu et al (Journal Cell Biology 1994 v127 pages 2081-2091 ...) and Laplantaine et al (Journal of Cell Science 2000 v113 1167-1176)." Applicants traverse the rejection.

Rieu refers to the binding site for neutrophil adhesion inhibitor NIF in β2 integrin complement receptor type 3 (CR3; CD11b) domain, that includes NAFKILVVITDGEK, named "A7" peptide. Laplantine refers to the intracellular domain of the β1 subunit that was generated to contain an additional N-terminal cysteine and immobilized on a carboxymethyl dextran sensorchip using thiol coupling. The chips were than exposed to solutions of α3 peptides. The thrust of Laplantine deals with α3β1 dominating α6β1 in interactions with extracellular ligands. Microcellular injections of α3 interfere with β1 cytoplasmic tails. The Examiner combines the references because both are allegedly drawn to methods of identifying interactive regions between integrins and interaction partners.

This combination does not support the rejection because the mere binding of a peptide to dextran does not teach a therapeutic conjugate, particularly because Laplantine refers to β1 subunit which is distinguishable from the β2 subunit. There would be no reason to combine the biosensor technology of Laplantine with the assays of Rieu. The Examiner states that the claims would have been obvious because a particular known technique (i.e. surface Plasmon resonance) was recognized as part of the ordinary capabilities of one of ordinary skill in the art. But this does not suggest the claimed peptide over any of the hundred of other peptides having integrin interactions.

More specifically, Rieu refers to the characterization of neutrophil adhesion inhibitor, NIF, a protein that inhibits neutrophil spreading and adhesion to endothelial cell monolayers by binding to CR3, a member of the β2 integrin subfamily expressed on activated neutrophils. Rieu hypothesizes that the A-domain of CR3 may be useful in treating hookworm infections by blocking NIF, which

allows the hookworm to evade the host's inflammatory response. Rieu states that "the binding cite for NIF in the CD11bA-domain is broad, comprised of primarily ***two*** centrally located ***overlapping*** peptides ***A6 and*** A7, with ***additional contribution by two peptides*** located at the beginning (A1) and end (A12) of the domain." (Emphasis added.)

These peptides, as shown on page 2089 of Rieu, include:

A1: CPQEDSDIAF LIDGSGSIIP

A6: TGIRKVVREL FNITNGAKN

A7: NAFKILVVIT DGEK

A12: HVFQVNNFEA LKTIQNQLRE

Hence, despite the presence of the amino acids of the instant claims in A7, Rieu actually ***teaches away*** from the specific 15-mer of the claims, because it teaches a binding cite comprising a "***broad interactive region***" combining of overlapping peptides of which A7 is only a part. Moreover, Rieu used peptides that were bound to a solid surface (page 2082, col. 2, page 2083, col. 1), and in no way suggests a therapeutic comprising the claimed peptide conjugated to a hydrophilic polymer.

Laplantine refers to the characterization of peptides representing the α3 or α6 integrin subunits for binding affinity to the β1 integrin subunit through surface plasmon resonance (SPR). For SPR, peptides corresponding to the integrin β1 cytoplasmic tail were covalently attached by thiol coupling to carboxymethyldextran (CM5) chips activated with a mixture of N-hydroxysuccinimide and N-ethyl-N'-dimethylaminopropyl carbodiimide followed by pyridinyldithioethaneamine. ***Alternatively***, the cytodomain of the integrin β1subunit in the form of a GST fusion protein was captured by polyclonal ***antibodies*** against GST immobilised onto a sensor chip through amine coupling using EDC/NHS chemistry. The soluble peptide corresponding to the α integrin subunit was flowed over the chip and the binding profiles were recorded.

Clearly, the context of Laplantine is directed to peptide immobilization to a chip, in which antibodies were used as well as carboxymethyldextran coupling. There is no suggestion that one might choose one technique (antibodies or carboxymethyldextran) over the other, or which one of those could possibly provide for a therapeutic bioconjugate. Importantly, the peptides of Laplantine were bound to the chip using an entirely different modes of binding chemistry, and Laplantine does not provide a reasonable expectation of success that the Applicants' different glycidyl methacrylate approach would yield a therapeutic bioconjugate.

The Examiner refers to Laplantine's Figure 7, but these data refer to surface Plasmon resonance analysis of the binding of α3 and β1 cytoplasmic tails, which data showed "a fast dissociation of α3 peptides from immobilized β1" (page 1173, col. 1). This provides no evidence that such binding would provide for an therapeutic bioconjugate. Indeed, a "fast dissociation" rate teaches away from the therapeutic bioconjugate of the instant claims.

Moreover, to the extent Laplantine provides any peptide sequences, these are distinct from the amino acid sequence of the instant claims:

Table 1. Peptide sequencing for the intracellular domains of the human α3A and α6A integrin subunits

α3A:	XGFFKRARTRALYEAKRQKAEMKSQPSETERLTDDY
α6A:	XGFFKRNKKDHYDATYHKAEIHAQPSDKERLTSDA
β1A:	gspef(X)KLLMIHDRREFAKFEKEKMNAKWDTGENPIY-KSAVTTVVNPKYEGK

compared to: CNAFKILVVITDGEK (SEQ ID NO:124)

Neither Rieu nor Laplantine, either individually or combined, suggest the particular amino acid sequence of the instant claims, or that this sequence when conjugated to a hydrophilic polymer provides for a therapeutic bioconjugate. Moreover, because Laplantine refers only to β1, there is no motivation to combine it with the Rieu reference that studied β2. Similarly, because Rieu derived peptides from NIF and β2 integrin, whereas Laplantine derived peptide from completely different sources, α (3 and 6) and β1 integrin, there is no motivation to combine these references.

The Court has instructed that "a patent composed of several elements is not proved obvious merely be demonstrating that each of its elements was, independently, known in the prior art." *KSR Int'l Co. v. Teleflex, Inc.*, 127 S.Ct. 1727, 1741 (2007). Regarding the pending claims, neither of the referenced provide, for example, for a therapeutic bioconjugate in with CNAFKILVVITDGEK is conjugated to a hydrophilic polymer. Hence, Applicants urge that the combination of Rieu and Palantine do not support a § 103 rejection, and request that this rejection be withdrawn.

CONCLUSION

For at least the reasons set forth above, Applicants respectfully submit that this application is in condition for allowance. Favorable consideration and prompt allowance of the claims are earnestly requested. The Commissioner is hereby authorized to charge any payment deficiency to Deposit Account No. 19-2380 referring to Attorney Docket No. 049954-004100.

Should the Examiner have any questions that would facilitate further prosecution or allowance of this application, the Examiner is invited to contact the Applicants' representative designated below.

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